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**Review Article**

# Alzheimer's Disease: A Comprehensive Review of Pathophysiology, Diagnosis, and Emerging Therapies

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## ABSTRACT

Alzheimer's disease (AD) remains the most common cause of neurodegenerative dementia worldwide, affecting millions of elderly individuals and imposing a significant socioeconomic burden. This review provides a comprehensive overview of the current understanding of AD, including its epidemiology, underlying pathophysiology, clinical presentation, diagnostic approaches, and available therapeutic strategies. The classic pathological hallmarks—extracellular amyloid-beta plaques and intracellular neurofibrillary tau tangles—are discussed alongside emerging concepts such as neuroinflammation, synaptic dysfunction, and vascular contributions. Current diagnostic methods, including neuroimaging and cerebrospinal fluid biomarkers, are evaluated, and the recent shift toward blood-based biomarkers is highlighted. This review also examines pharmacological interventions, including cholinesterase inhibitors, NMDA receptor antagonists, and recently approved anti-amyloid immunotherapies, as well as non-pharmacological and lifestyle-based preventive approaches. The findings reinforce that early detection and multi-domain lifestyle interventions represent the most promising strategies for delaying disease progression. The review concludes that a paradigm shift toward combination therapies and precision medicine is essential to address the multifactorial nature of Alzheimer's disease

## INTRODUCTION

Alzheimer's disease (AD) is a progressive, irreversible neurodegenerative disorder characterized by gradual decline in cognitive function, memory loss, and eventual inability to perform daily activities [1]. It is the most prevalent form of dementia, accounting for 60–80% of all dementia cases globally [2]. First described by Dr. Alois Alzheimer in 1906, the disease has since become a major public health priority as populations age worldwide [3].

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According to the World Health Organization (WHO), approximately 55 million people are living with dementia globally, and nearly 10 million new cases are diagnosed each year [4]. Alzheimer's disease contributes to 60–70% of these cases. The global economic burden of dementia was estimated at $1.3 trillion USD in 2019, a figure projected to rise to $2.8 trillion by 2030 [5]. In India, the prevalence of AD is increasing rapidly, with an estimated 5.3 million people over the age of 60 living with dementia, a number expected to triple by 2050 [6].

The disease is classified into two main forms: early-onset familial AD (accounting for less than 5% of cases), which manifests before age 65 and is linked to autosomal dominant mutations in genes such as amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2); and late-onset sporadic AD (over 95% of cases), which typically presents after age 65 and results from a complex interplay of genetic, environmental, and lifestyle factors [7, 8].

Despite decades of research, no cure currently exists for Alzheimer's disease. However, recent advances in biomarker development, neuroimaging, and disease-modifying therapies have transformed the landscape of AD diagnosis and treatment, offering new hope for early intervention and improved patient outcomes [9].

## 2. EPIDEMIOLOGY

Alzheimer's disease demonstrates a clear age-related increase in prevalence and incidence. The prevalence doubles approximately every five years after age 65, rising from 3% among individuals aged 65–74 years to nearly 32% among those aged 85 years and older [10]. Women are disproportionately affected, comprising nearly two-thirds of all AD patients, partly due to their longer life expectancy and potential hormonal factors [11].

Geographically, the highest prevalence rates are observed in Western Europe and North America, followed by Latin America and China [12]. However, the fastest growth in AD cases is occurring in low- and middle-income countries, where healthcare infrastructure for dementia care remains limited [13]. By 2050, nearly 70% of all dementia cases are projected to reside in low- and middle-income countries [14].

The major risk factors for AD are categorized as non-modifiable and modifiable. Non-modifiable risk factors include advancing age, female sex, and genetic predisposition, particularly the apolipoprotein E (APOE) ε4 allele [15]. Individuals carrying one copy of APOE ε4 have a 3- to 4-fold increased risk, while those with two copies have a 10- to 15-fold increased risk [16]. Modifiable risk factors, as identified by the Lancet Commission on dementia prevention, account for approximately 40% of dementia cases worldwide and include lower education, hearing loss, hypertension, obesity, smoking, depression, physical inactivity, social isolation, diabetes, excessive alcohol consumption, air pollution, and traumatic brain injury [17].

## 3. PATHOPHYSIOLOGY

The pathophysiology of Alzheimer's disease is complex and multifactorial, involving several interconnected molecular and cellular mechanisms that culminate in progressive neuronal loss and brain atrophy.

### 3.1 Amyloid Cascade Hypothesis

The amyloid cascade hypothesis remains the dominant framework for understanding AD pathogenesis [18]. According to this hypothesis,

the accumulation of amyloid-beta (Aβ) peptides is the primary initiating event in AD. Aβ is derived from the sequential proteolytic cleavage of amyloid precursor protein (APP) by β-secretase (BACE1) and γ-secretase [19]. In AD, an imbalance between Aβ production and clearance leads to the aggregation of Aβ monomers into soluble oligomers, which are considered the most neurotoxic species, and subsequently into insoluble fibrils that deposit as senile plaques [20, 21].

Soluble Aβ oligomers impair synaptic plasticity, disrupt long-term potentiation (LTP), and trigger inflammatory responses long before plaque deposition becomes detectable [22].

### 3.2 Tau Pathology and Neurofibrillary Tangles

Hyperphosphorylation of the microtubule-associated protein tau leads to its detachment from microtubules, aggregation into paired helical filaments, and formation of intracellular neurofibrillary tangles (NFTs) [23]. Unlike amyloid plaques, the spread of tau pathology correlates more closely with the pattern and severity of cognitive decline [24]. Tau pathology follows a stereotypical progression: first appearing in the transentorhinal region (Braak stage I-II), spreading to the limbic system including the hippocampus (Braak stage III-IV), and eventually involving neocortical association areas (Braak stage V-VI) [25].

### 3.3 Neuroinflammation

Chronic neuroinflammation is now recognized as a key driver of AD progression rather than merely a consequence of pathology [26]. Activated microglia and reactive astrocytes surround amyloid plaques, releasing pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) [27]. Genetic studies have identified variants in immune-related genes that increase AD risk, including TREM2 and CD33, underscoring the role of innate immunity in disease pathogenesis [28, 29].

### 3.4 Vascular Dysfunction

Vascular contributions to AD are increasingly appreciated. Cerebral hypoperfusion, blood-brain barrier (BBB) disruption, and reduced amyloid clearance via perivascular drainage pathways accelerate disease progression [30]. Cardiovascular risk factors such as hypertension, diabetes, hypercholesterolemia, and obesity in midlife are associated with higher AD risk [31].

## 4. CLINICAL FEATURES AND STAGES

Alzheimer's disease typically follows a progressive course spanning 8–12 years from diagnosis to death, although the trajectory can vary considerably [32].

Preclinical AD: This stage is characterized by the presence of AD pathology on biomarkers in the absence of overt clinical symptoms. This stage may last 15–20 years before symptom onset [33].

Mild Cognitive Impairment (MCI) due to AD: Patients experience cognitive decline beyond what is expected for their age and education level, but functional abilities remain largely intact. Memory impairment is the most common presentation [34].

Mild AD Dementia: Cognitive deficits interfere with daily activities. Common features include short-term memory loss, difficulty with problem-solving, word-finding difficulties, getting lost in familiar places, and mood changes [35].

Moderate AD Dementia: Cognitive decline becomes more pronounced. Patients require assistance with daily activities. Behavioral and

psychological symptoms of dementia (BPSD), including agitation, wandering, delusions, and hallucinations, frequently emerge [36].

Severe AD Dementia: Patients lose the ability to communicate and become completely dependent on caregivers. Death typically results from complications such as aspiration pneumonia [37].

## 5. DIAGNOSIS AND BIOMARKERS

The diagnosis of Alzheimer's disease has evolved from purely clinical assessment to a biological framework incorporating biomarkers. The National Institute on Aging and Alzheimer's Association (NIA-AA) proposed the AT(N) classification system [38].

**Neuroimaging:**

- Structural MRI reveals medial temporal lobe atrophy, particularly hippocampal volume loss [39].
- Amyloid PET uses tracers to visualize fibrillar amyloid plaques. A negative scan effectively rules out AD pathology [40].
- Tau PET tracers bind to neurofibrillary tangles and demonstrate strong correlation with clinical severity [41].
- FDG-PET reveals hypometabolism in temporoparietal and posterior cingulate regions [42].

**Fluid Biomarkers:**

- Cerebrospinal fluid (CSF) biomarkers demonstrate high diagnostic accuracy. The characteristic AD profile includes reduced Aβ42/40 ratio and elevated phosphorylated-tau (p-tau) and total-tau (t-tau) [43].
- Blood-based biomarkers represent a recent breakthrough. Plasma p-tau181, p-tau217, and p-tau231 demonstrate excellent correlation with CSF and PET findings [44].

## 6. CURRENT THERAPEUTIC STRATEGIES

### 6.1 Symptomatic Treatments

Cholinesterase inhibitors (donepezil, rivastigmine, galantamine) increase acetylcholine availability. These agents provide modest symptomatic benefit for mild-to-moderate AD [45].

Memantine, an NMDA receptor antagonist, modulates glutamate-mediated excitotoxicity and is indicated for moderate-to-severe AD [46].

### 6.2 Disease-Modifying Therapies

Recent regulatory approvals mark a paradigm shift:

Lecanemab (Leqembi™) is a humanized monoclonal antibody targeting soluble Aβ protofibrils. In the Phase 3 Clarity AD trial, lecanemab reduced brain amyloid burden and slowed cognitive decline by 27% over 18 months, leading to full FDA approval in 2023 [47].

Donanemab (Kisunla™) targets deposited Aβ plaques. In the TRAILBLAZER-ALZ 2 trial, donanemab slowed cognitive decline by 35% in early-stage patients, with FDA approval granted in 2024 [48].

These anti-amyloid immunotherapies carry risks of amyloid-related imaging abnormalities (ARIA), necessitating regular MRI monitoring [49].

## 7. PREVENTION AND LIFESTYLE INTERVENTIONS

Given the absence of a cure, prevention is critical. Multi-domain lifestyle interventions targeting multiple risk factors simultaneously have shown particular promise [50].

The landmark FINGER trial demonstrated that a 2-year multidomain intervention including nutritional guidance, physical exercise, cognitive training, and management of vascular risk factors improved cognitive function in at-risk older adults [51].

Specific preventive strategies include:

- Cognitive engagement (education, mentally stimulating activities) [52]
- Physical activity (aerobic exercise, 150 minutes per week) [53]

· Dietary patterns (Mediterranean diet, MIND diet) [54]

- Vascular risk factor control [55]
- Hearing rehabilitation [56]
- Smoking cessation [57]

## 8. CONCLUSION

Alzheimer's disease remains one of the greatest public health challenges of the 21st century, with rising prevalence, substantial caregiver burden, and no cure currently available [58]. Significant advances have been made in understanding the molecular mechanisms driving AD, including the roles of amyloid-beta, tau, neuroinflammation, and vascular dysfunction. The development of sensitive fluid and imaging biomarkers has transformed diagnosis, enabling earlier detection. The recent approval of anti-amyloid immunotherapies represents a paradigm shift toward disease modification [59].

The greatest immediate opportunity lies in risk reduction through public health strategies targeting modifiable lifestyle and cardiovascular risk factors. Moving forward, successful management of AD will require integrated approaches combining pharmacological and non-pharmacological strategies, delivered within a framework of precision medicine [60].

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